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(54) Title: ORAL FORMULATION FOR HYDROPHILIC DRUGS

(57) Abstract

The present invention relates to a pharmaceutical composition and concentrate suitable for oral administration comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid, and water; an oral formulation comprising uniform dispersion of the pharmaceutical concentrate in an aqueous phase optionally comprising a self–emulsifying material; and to a process of making the same.

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ORAL FORMULATION FOR HYDROPHILIC DRUGS

Technical Field

The present invention relates to a pharmaceutical composition and formulation concentrate suitable for oral administration comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water; a uniform dispersion of the formulation concentrate in an aqueous phase optionally comprising a self-emulsifying material and to a process of making the oral formulations with unexpectedly high concentrations of the hydrophilic drug in the lipophilic phase.

Background of the Invention

Oral administration of liquid dosage forms is a particularly useful route of administration of therapeutic agents. However, administration of many compounds by these routes is not acceptable due to poor bioavailability of the therapeutic agent. Orally administered therapeutic agents are rapidly transported to the stomach and small intestine for absorption across the gastro-intestinal mucosal membranes into the blood. The efficiency of absorption of a therapeutic agent (i.e. the ratio of the amount entering the blood to the amount administered) following oral administration of many drugs can be low because of several factors which serve to metabolize the administered chemical. Therefore, if the preferred route of administration is the oral route, it is often necessary to administer large dosages of the compounds. This is costly and in many cases inefficient. Such therapeutic agents can be administered via other routes such as intravenously, subcutaneously, or intraperitoneally, but these alternatives are all invasive by nature and can involve pain and discomfort to the patient.

A particularly useful class of compounds are peptides of twenty or less amino acid residues. Recent pharmaceutical research has led to the discovery of many synthetic peptides in this class which are effective therapeutic agents. Noteworthy among these synthetic small peptides are compounds which act as either agonists or antagonists of gonadotropin releasing hormone (GnRH, also known as "luteinizing hormone releasing hormone, LHRH), and peptides ~~or p~~eptide like compounds of twenty residues or less which act to inhibit renin and are thus effective as agents for treating hypertension and related disease conditions of the cardiovascular system. A number of small peptides and modified peptides have also been found which act to modulate the natural peptide C5a.

While the discovery of peptide compounds having therapeutic value has moved rapidly in the last few years, the development of viable drug delivery systems for many of these compounds has often proven to be problematic. The gastrointestinal tract secretes a variety of agents that metabolize polypeptides. Exemplary of such catabolic agents are pepsin, trypsin,

chymotrypsin, carboxypolypeptidases, aminopolypeptidases and dipeptidases. Polypeptides that escape catabolism in the stomach and small intestine are transported across the cells lining of the gastrointestinal tract into the portal circulation, which carries absorbed polypeptides to the liver. Absorbed polypeptides are subject to further degradation by a myriad of hepatic metabolic events. Such hepatic degradation of absorbed materials from the blood before such materials enter the general systemic circulation is known in the pharmaceutical art as the "first pass effect". Therefore, most, if not all, of these compounds must be administered parenterally as, for example, subcutaneous, intramuscular, or intraperitoneal injection. Since most patients cannot self-administer parenteral drug formulations, it is frequently necessary that drugs of this type be administered in an out-patient setting leading to additional costs associated with their use.

Several U.S. Patents, for example, 4,652,441; 4,652,443; 4,711,782; 4,917,893; 5,061,492; 5,330,767; 5,476,663, 5,480,656, and 5,643,607 disclose prolonged release microcapsule comprising a polypeptide in a polymer matrix, and methods of preparing the same.

U.S. patent application, Serial No. 08/693,724, filed August 7, 1996 discloses uniform dispersions comprising a water-soluble drug, a self-emulsifying material, an oil and a short chain alcohol which are suitable for oral administration. The uniform dispersions described in the above application comprise substantial amounts of a non-fatty acid oil and require micronization or repeated homogenization to obtain uniform dispersion of the suspended drug and do not possess the optimum stability towards the enzymatic degradation for prolonged periods of time.

There is, therefore, a pressing need for new, more stable, efficient, cost effective, and easier to prepare formulations, suitable for oral administration, which are easily administered to patients, are stable towards enzymatic degradation, increase the permeability of the drug and effect the desired bioavailability of the therapeutic agent.

Summary of the Invention

Hydrophilic drugs when administered orally as aqueous formulations undergo enzymatic degradation resulting in very poor bioavailability of the drug to the patient. The poor oral availability of these drugs may be due to the high molecular weight, low lipophilicity and enzymatic instability. *In vitro* tests have demonstrated that some hydrophilic drugs, specifically leuprolide acetate are easily degraded by gastrointestinal enzymes. Hydrophilic drugs, specifically leuprolide acetate have low solubility in lipids, thereby limiting the use of oil formulations.

The present invention relates to the surprising solubilization of hydrophilic drugs, such as leuprolide acetate in fatty acids such as oleic acid, a C_{18} fatty acid lipid system, thereby

protecting the drug from enzymatic degradation in the GI tract and increasing the bio-availability, thus making oral administration of the hydrophilic drug desirable.

Surprisingly this increased solubilization can only be achieved by partitioning the drug between an aqueous buffer and a fatty acid. A linear relationship has been found between the amount of leuprolide acetate which can be extracted into the oleic acid and initial concentration of leuprolide acetate in the aqueous solution.

The solubility of leuprolide acetate in oleic acid, for example, is less than 0.01 mg/mL. However, when a fatty acid is added to a solution of leuprolide acetate in water, the solubility of the drug in the lipophilic phase increases to greater than about 200 mg/mL, which is exponentially higher than the solubility of leuprolide acetate in oleic acid alone.

This unexpected solubility phenomenon has been employed by using a small amount of water with a high concentration of leuprolide acetate to achieve significant solubilization of leuprolide acetate in oleic acid to obtain a formulation concentrate.

The present invention, thus, relates to formulation concentrates and oral formulations comprising hydrophilic drugs in a lipophilic phase and methods of preparing the formulations with unexpectedly high concentrations of the drug in the lipophilic phase.

In one aspect of the invention, therefore, the present invention relates to a pharmaceutical composition concentrate, suitable for oral administration, comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

In another aspect, the present invention relates to a pharmaceutical composition, suitable for oral administration, comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

In still another aspect, the present invention relates to an oral pharmaceutical composition comprising:

a pharmaceutical concentrate dispersed in an aqueous phase optionally comprising a self-emulsifying material, wherein the concentrate comprises a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

In yet still another aspect, the present invention relates to a process for preparing a pharmaceutical formulation concentrate, suitable for oral administration, comprising:

dissolving a hydrophilic drug in water; and

extracting the hydrophilic drug into a fatty acid.

The formulations of the invention are stable towards enzymatic degradation, and are easy to prepare and administer to the patients.

Brief Description of the Drawings

FIGURE 1 is a plot of log % leuprolide acetate remaining vs time in hours following the addition of trypsin to various formulations of the invention individually containing a

different fatty acid. The Figure illustrates the enzymatic degradation profiles of the formulations of the invention as compared to the formulation containing olive oil and to the aqueous leuprolide acetate solution.

FIGURE 2 is a plot of log % leuprolide acetate remaining vs time in hours following the addition of trypsin to various formulations of the invention individually containing a different alcohol. The Figure illustrates the enzymatic degradation profiles of the formulations of the invention as compared to the formulation containing no alcohol and to the aqueous leuprolide acetate solution.

FIGURE 3 is a plot of plasma concentration in ng/mL vs time in minutes following the oral administration to fasted rats of the formulation of the invention. The filled-in diamonds represent the aqueous leuprolide acetate solution and the filled-in squares represent the formulation of the invention.

FIGURE 4 is a plot of leuprolide concentration in mg/mL in aqueous and oleic acid layers vs the initial drug level in mg/mL. The hollow circles represent the aqueous layer and the filled-in squares represent the oleic acid layer. The Figure illustrates the leuprolide concentration in oleic acid following the extraction from aqueous acetate solutions (pH 5) at various concentrations of leuprolide.

FIGURE 5 is a correlation plot of the infrared response of leuprolide acetate in oleic acid layer vs. initial leuprolide concentrate in mg/mL of the solution after the extraction of leuprolide acetate from the aqueous solution at pH 5 into the oleic acid.

Detailed Description of the Invention

The term "hydrophilic drug" as used herein means a drug which has a low oil/water partition ratio. The term "low oil/water partition" ratio means that the octanol/water partition ratio, for example, is no greater than about 0.1.

The term "extraction/partitioning" as used herein means the extraction or partitioning of a hydrophilic drug from its solution in a water/alcohol co-solvent system into the fatty acid. In other words, it means the solubility of the drug in the fatty acid. The terms extraction, partitioning and solubility are used interchangeably herein.

The hydrophilic drugs can be any type of water-soluble drugs. Illustrative of the water-soluble drugs include, but are not limited to, biologically active polypeptides, antibiotics, antitumor agents, antipyretics, analgesics, antiinflammatory agents, antitussives and expectorants, sedatives, muscle relaxants, antiepileptics, antiulcer agents, antidepressant, antidiabetics, diuretics, hormone drugs, renin inhibitors, $C5_a$ agonists and antagonists and the like.

The preferred hydrophilic drugs for the purposes of this invention are the biologically active polypeptides. The biologically active polypeptides are preferably those having a

molecular weight between about 200 and about 8,000. Examples of the peptides include polypeptides which have a pharmacological or psychological action in an animal subject to affect lutenizing hormone release hormone (LHRH), to inhibit the action of renin, or to modulate the physiological activity of C5a.

The preparation and therapeutic use of suitable peptide agonists and antagonists of LHRH comprising from three to ten aminoacid residues for the formulation concentrates and the oral formulations in accordance with the present invention are disclosed in, for example, U.S. Patent Nos. 3,787,385; 3,790,555; 3,826,794; 3,880,825; 3,915,947 3,953,416; 3,963,691; 3,974,135; 4,003,884; 4,008,209;4,022,759, 4,022,760; 4,022,761; 4,071,622, 4,024,248; 4,072,668; 4,075,189; 4,075,192; 4,234,571; 4,244,946; 4,253,997; 4,318,905; 4,800,191; and 5,198,533.

Particularly preferred LHRH-active peptides and peptide like compounds for inclusion in formulations of the present invention include the following compounds and their pharmaceutically acceptable salts:

N-acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyltyrosyl-D-N^e-nicotinoyllysyl-L-leucyl-L-N^e-isopropyllysyl-L-prolyl-D-alanylamide acetate, disclosed in United States Patent 5,110,904,

5-oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tyrosyl-D-leuyl-L-leuyl-L-arginyl-L-prolylethylamide, also known by the generic name leuprolide, disclosed in United States Patent 4,005,063.

Renin inhibitor compounds suitable for formulations of the present invention are disclosed, for example, in the United States Patent Nos. 4,384,994; 4,470,971; 4,477,440; 4,477,441; 4,474,941; 4,478,826; 4,560,505; 4,595,677; 4,636,491; 4,665,193; 4,698,329; 4,722,922; 4,746,648; 4,749,687; 4,749,781; 4,818,748; 4,837,204; 4,857,507; 4,863,903; 4,863,904; 4,863,905; 4,864,017; 4,874,745; 4,880,781; 4,895,834; 5,268,374.

Preferred renin inhibitors for incorporation into the formulations of the present invention include:

((beta,beta, dimethyl)beta-Ala-4-(CH_3O)-Phe-His-(2S-amino-1-cyclohexyl-3R,4S-dihydroxy-6-methyl))heptane, also known by the generic name enalkiren, disclosed in United States Patent 4,845,079;

2S-2-benzyl-3-((1-methylpiperazin-4-yl)sulfonyl)propionyl-4-thial-(2S-amino-1-cyclohexyl-3R,4S-dihydroxy-6-methyl)heptane, also known by the generic name zankiren, disclosed in published European Patent Application No. EP 456 189, published November 13, 1991;

2S,1S-(4-methoxymethoxypip ridin-1-yl)carbonyl-2-phenylethoxyhexanoic acid amide of 3-(4-morpholinyl)propyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanamide, disclosed in United States Patent 5,268,374; and

1S-(4-(methoxymethoxypiperidin-1-yl)carbonyl)-2-phenylethyl-L-norleucyl amide of 3-(4-morpholinyl)propyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanamide, disclosed in United States Patent 5,268,374.

C5a agonists and antagonists suitable for incorporation into formulations of the present invention are disclosed United States Patent Nos., for example, 4,692,511; 5,190,922 ; 5,223,485.

Illustrative of antibiotics suitable for incorporation into formulation for the present invention include, but are not limited to, gentamycin, tetracycline hydrochloride, amkacin, fradiomycin, sisomicin, oxytetracycline, amphicillin, piperacillin, cefoperazone, and the like.

The fatty acids suitable for extracting the hydrophilic drugs from the aqueous phase are those having from C_5 to C_{25} carbon chain. It has been found that the amount of drug that is extracted in the fatty acid depends upon the pH of the concentrate and the length of the carbon chain of the fatty acid. Not being bound by theory, it is believed that this may be due to the fact that the polarity decreases with an increase in the chain length of the fatty acid. Shorter the chain length of the fatty acid, and lower the buffer pH, higher is the extraction of the drug into the fatty acid.

The extraction of the hydrophilic drug is pH dependent because the drug ionizes in water to a degree depending on the pH of the solution. The pH of the aqueous solution used for extraction ranges from about 2 to about 8. The solubility of leuprolide acetate in oleic acid, for example, increases to greater than 200 mg/mL of the concentrate with an increase in the pH of the aqueous solution used for partitioning. By contrast, the solubility of the hydrophilic drug such as leuprolide acetate, is near 0 in olive oil or in 1-octanol even at pH 0 .

The amount of fatty acid generally varies from about 10% to about 99.8% of the volume of the concentrate. Preferably, the amount of the fatty acid varies from about 30% to about 45% by the volume of the concentrate. Most preferably, the amount of fatty acid is about 40% by volume of the concentrate. The most preferred fatty acid for the purposes of this invention is oleic acid.

The amount of water in the concentrate can vary from about 0.2% to about 20% of the volume ~~of the~~ concentrate. Preferably, the amount of water varies from about 0.5 to about 2% of volume of the concentrate.

The formulation concentrate comprising a hydrophilic drug, water and oleic acid may result in a physically unstable two-phase formulation which is generally an unacceptable dosage form. The formulation concentrate desirably comprises a C_1-C_5 alcohol. The alcohols suitable for the formulations of the invention are selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, isobutanol, t-butanol, n-pentanol, iso-pentanol, and neo-pentanol. The most preferred alcohol is ethanol. The amount of alcohol in the concentrate can vary from 0% to about 60% of the volume of the concentrate. If the

amount of alcohol is 0%, a self-emulsifying material with hydrophile-lipophile balance (HBL) of greater than 10 is added to the two-phase mixture of water, drug and the fatty acid to obtain a one-phase concentrate. When no self-emulsifying material is added, the amount of alcohol may vary from about 0.2% to about 50% by the volume of the concentrate. Preferably, the amount of alcohol varies from about 2% to about 10% of the volume of the concentrate.

The formulation concentrate desirably further comprises a self-emulsifying material to facilitate the emulsification of the concentrate in aqueous vehicles. Suitable self-emulsifying materials are those with HLB of 10 or over and are selected from the group consisting of Tween-20, Tween 80, Cremophor EL-P, and Cremophor RH-40. The amount of the self-emulsifying material varies from about 10% to about 90% of the volume of the concentrate. Preferably the amount of the self-emulsifying material is about 40%-50% of the volume of the concentrate. The most preferred self-emulsifying material suitable for the formulation is Tween-80. The volume/volume ratio of the fatty acid to the self-emulsifying material varies from about 1:0 to about 1:4. The most preferred volume/volume ratio of the fatty acid to the self-emulsifying material is from about 1:01 to about 1:1.

The formulation concentrate may also contain additional agents such as preservatives and antioxidants. Typical preservatives include sodium benzoate, sorbic acid, and the methyl and propyl esters of *p*-hydroxybenzoic acid (parabens). Representative antioxidants include vitamin E, butylated hydroxy anisole, butylated hydroxy toluene, nordihydroguaiaretic acid, the gallates such as propyl gallate, hydroquinone, propenyl methyl guaethol and alkyl thiopropionates, or water soluble agents such as alkanolamines, alcohols, and propylene glycol.

The formulation concentrates may further comprise sweetening agents and flavoring agents such as menthol, fruit flavoring and the like to make the formulation palatable to the patients.

The formulation concentrate suitable for oral administration is prepared by first dissolving a hydrophilic drug in water and preferably in a water and alcohol co-solvent system. Desired amounts of a fatty acid, and optionally a self-emulsifying material are then mixed until a clear yellowish oily solution is obtained.

A basic preferred formulation concentrate comprises the following ingredients:

Drug	50 mg
Water	0.2 mL
Ethanol	1.0 mL
Oleic Acid	4.0 mL
Tween-80	4 mL

qs with Tween-80 to obtain 10 mL of the concentrate.

A preferred formulation concentrate comprises the following ingredients:

Leuprolide Acetate	50 mg -100 mg
Water	0.2 mL
Ethanol	1.0 mL
Oleic Acid	4.0 mL
Polysorbate, NF (Tween-80)	4.0 mL
Prosweet	0.1 mL
Butylated Hydroxy Toluene (BHT)	0.01 mL
Menthol	0.2 mL
Methyl Paraben	10.0 mg
qs to 10 mL with Tween-80	

The oral formulations of the invention are obtained by adding the concentrate into an aqueous medium optionally comprising a self-emulsifying material and vortexing the mixture for a few minutes by the methods known in the art. The self-emulsifying material is added to the aqueous phase in those instances where there is no such material originally present in the concentrate. The aqueous medium is selected from the group consisting of milk; fruit juice; water, and an aqueous solution comprising an excipient selected from the group consisting of aspartame, glucose, mannitol, sorbitol, sugar, sucrose and lactose. The amount of drug in the oral formulations can vary from about 0.1mg/1mL to about 500 mg/mL, based on the volume of the concentrate. Preferably, the amount of drug in the formulations varies from about 1.0 mg/mL to about 20 mg/mL, based on the volume of the concentrate. The choice of an aqueous medium and its volume for dispersion of the concentrate depends on various factors including the type of drug, the individual preferences and the prescription for the individual patient in need of the treatment.

Alternatively, pharmaceutically acceptable soft elastic capsules may be filled with from about 0.1 mL to about 1.0 mL of the formulation concentrate and orally administered as needed.

The invention is best understood by the following Examples which are merely illustrative and are not to be construed as limitative of the invention.

Examples

Example 1

Stability of Leuprolide Acetate in the Formulation towards *in-vitro* Enzymatic Degradation

Effect of the various fatty acids

To compare the effect of oleic acid with other fatty acids and a non fatty acid oil on the stability of leuprolide acetate towards *in-vitro* enzymatic degradation, a study using Trypsin (50 mM Tris and 1.0 mM Dethiothreitol, pH 7.4) was conducted by methods known in the art. Oral formulations containing n-caproic acid, caprylic acid, palmitoleic acid, oleic acid, linolenic acid, and olive oil, respectively, were tested. An aqueous formulation of leuprolide acetate in a saline solution was used as a control. The amounts of the various ingredients used were the same as the basic formulation: leuprolide acetate 5 mg/mL (w/v); fatty acid or olive oil 40% (v/v); Tween-80 40% (v/v); water 2% (v/v); ethanol 10% (v/v); q.s. with Tween-80.

The results of the study are illustrated in Figure 1 by plotting log % leuprolide acetate remaining vs time in hours following the addition of trypsin to the formulation. The % leuprolide acetate remaining was determined by HPLC using a C_{18} column and 0.087 M ammonium phosphate buffer at pH 6.5 (26%)/acetonitrile (74%).

The results indicate that the formulations of the invention are significantly more stable towards the enzymatic degradation than the formulation containing olive oil and the control. In other words, the various fatty acid in the formulations protect the drug from enzymatic degradation when compared to formulations in olive oil or to the aqueous leuprolide solution.

Effect of various alcohols

Six basic formulations were prepared using the amounts of various ingredients as described above and tested for enzymatic degradation. Each of the formulations contained leuprolide acetate, water, oleic acid, Tween and 1 mL (10% v/v) of one of the following: methanol, ethanol, isopropyl alcohol, 1-butanol, and 1-pentanol. One formulation contained 12% water (v/v) and 0% alcohol as the only solvent. A saline solution of leuprolide acetate was used as a control.

The results of the study are illustrated in Figure 2 by plotting log % leuprolide acetate remaining vs time in hours following the addition of trypsin to the formulation. The results indicate that the formulations containing water alone or alcohols are significantly more stable towards enzymatic degradation than the saline solution of leuprolide acetate.

Example 2

Oral Drug Bioavailability of the Formulations in Sprague Dawley Rats

Male Sprague-Dawley rats, each weighing about 300 g at the time of the experiment, were used for the experiment. Each rat was fasted overnight. A dose of 3 mg-kg of the formulation containing 50 mg leuprolide acetate, water 0.2 mL, ethanol 1.0 mL, oleic acid 4.0 mL, q.s. to 10 mL with Tween-80 was administered by gavage using intubation of formulations into the stomach. About 0.3 mL blood samples were collected under ether anesthesia via jugular venipuncture. Blood samples were placed into microcentrifuge tubes containing 50 μL of 15% K3EDTA as anticoagulant. Samples were then mildly agitated by shaking and spun down for ten minutes at 5000 rpm in a Beckman Microfuge-12. Blood samples were collected prior to dosing and also at 5, 15, 30, 60, 120, 180, 300, 480, and 1440 minutes after dosing. Plasma samples were frozen at -10°C to -20°C until assayed. Drug concentrations in plasma samples were measured by radioimmunoassay.

Plasma concentrations in ng/mL vs time in minutes following oral administration of leuprolide acetate formulation are plotted in Figure 3. The filled-in diamonds represent the concentration of the aqueous leuprolide solution and filled-in squares represent the concentration of the formulation of the invention. The Figure demonstrates that the oral formulation of the invention has improved bioavailability of leuprolide over the aqueous leuprolide solution.

Example 3

Extraction of leuprolide acetate into fatty acids at various pHs

Five buffer solutions at 0.1 M strength at various pHs, namely, pH 2 phosphate buffer, pH 3 phosphate buffer, pH 4 acetate buffer, pH 5 acetate buffer, and pH 7.5 phosphate buffer were employed in this example. 1.2 mL of each buffer solution containing leuprolide acetate was placed into a centrifuge tube. 0.2-0.3 mL of one of the following: valeric acid, isovaleric acid, n-caproic acid, heptanoic acid, caprylic acid, palmitoleic acid, linoleic acid, oleic acid, olive oil, or 1-octanol was added to individual centrifuge tubes. After being vortexed, the tubes were centrifuged at 10,000 rpm for five minutes. 0.1 mL of the aqueous layer was transferred into a 10 mL volumetric flask and diluted to volume with methanol containing 0.1% perchloric acid. The leuprolide concentration in each individual buffer solution was then assayed by HPLC. The results are set forth in Table 1 below.

Table 1

Oil Phase	Leuprolide Concentration									
	pH 2		pH 3		pH 4		pH 5		pH 7.5	
	Aqueous µg/mL	Oil µg/mL	Aqueous µg/mL	Oil µg/mL	Aqueous µg/mL	Oil µg/mL	Aqueous µg/mL	Oil µg/mL	Aqueous µg/mL	Oil µg/mL
Valeric Acid $C_5H_{10}O_2$	365	7570	40	10276	38	11053	13	9164	24	8986
Isovaleric Acid $C_5H_{10}O_2$	607	6123	220	9193	74	10836	55	8913	58	8779
n-caprioic Acid $C_6H_{12}O_2$	1118	3056	47	10230	12	11206	3	9221	1	9123
Heptanoic Acid $C_7H_{14}O_2$	1592	212	131	9730	6	11242	21	9113	30	8952
Caprylic Acid $C_8H_{10}O_2$	1523	626	335	8501	206	10043	8	9190	14	9045
Palmitoleic Acid $C_{16}H_{30}O_2$	1521	635	1728	143	1577	1819	11	9173	27	8965
Linolenic Acid $C_{18}H_{30}O_2$	1613	87	1723	176	1764	803	7	9199	7	9088
Oleic Acid $C_{18}H_{34}O_2$	1538	535	1777	~0	1849	185	10	9179	11	9062
Olive Oil	1651	~0	1856	~0	1804	457	1507	197	1501	125
1-Octanol $C_8H_{18}O_2$	1563	385	1757	~0	1885	~0	1550	~0	1521	2
Buffer Solution	1627	-	1752	-	1880	-	1540	-	1522	-

The results in Table 1 demonstrate that the drug concentration in the aqueous layer decreased with increasing buffer pH. At pH 5 and 7.5, only trace amounts of leuprolide acetate were detected in the aqueous layer, indicating that the majority of the drug was extracted into the fatty acid layer. On the other hand, the leuprolide acetate concentration in 1-octanol and olive oil were found to be unchanged at all the pHs, indicating that the drug was not extracted into 1-octanol or olive oil from the aqueous layer under any pH condition.

Example 4

Extraction of leuprolide acetate into oleic acid at pH 5

Five buffer solutions at 0.1M strength at pH 5, each containing 1.67, 7. 5, 15, 30, and 60 mg/mL, respectively, were prepared. 1.2 mL of each of the solution was treated according to the method described in Example 3. The leuprolide concentration in the aqueous layer was assayed by HPLC. The solubility of leuprolide in oleic acid is 0.152 mg/mL. The results are set forth in Table 2 below.

Table 2

Extraction of Leuprolide to Oleic Acid from an Aqueous Solution at pH 5

$C_{initial}$ mg/mL	C_{water} (HPLC) mg/mL	C_{oil} (calculated*) mg/mL
1.67	0.01	9.18
7.95	1.27	40.08
15.35	2.48	77.22
31.62	6.20	152.52
60.56	20.18	242.28

*Calculation: $C_{oil} = (C_{initial} - C_{water}) X 1.2/0.2$

The results demonstrate that the drug concentration is much higher in the oleic acid than that in the aqueous layer thereby increasing the protection of the drug by the oleic acid.

The results of the study are further illustrated in Figure 4 by plotting leuprolide acetate concentration in mg/mL vs various concentrations of leuprolide acetate. The results indicate that the concentration of leuprolide acetate in the oleic acid layer increases with an increase in the concentration of oleic acid in the formulation.

Example 5

Infrared Spectroscopy for the determination of the concentration of leuprolide acetate in oleic acid

The determination of the relative leuprolide acetate concentrations in the oleic acid layer of extraction preparations of Example 3 was performed by comparing the peak area of the IR spectral amide I band as described in B. Stuart, "Biological Applications of Infrared Spectroscopy (ACOL)", John Wiley and Sons, 1997, pp 114-115. A Nicolet Magna-IR model

750 spectrometer was used for the analysis. All samples were analyzed as a thin film between two sodium chloride discs (25x4 mm). A Spectra-Tech InspectIR, video microanalysis accessory, with a Germanium attenuated total reflection (Ge ATR) crystal was used to obtain a reference spectrum of a pure leuprolide acetate sample. Identification of leuprolide acetate in each oleic acid layer was accomplished by electronic subtraction of the pure oleic acid IR spectrum from the sample IR spectrum. All sample IR subtraction spectra were qualitatively similar to the reference IR spectrum of leuprolide acetate.

The results are illustrated in Figure 5 by plotting the infrared responses of leuprolide acetate in oleic acid layer versus initial leuprolide acetate concentration. The Figure demonstrates a linear dependence between the amount of leuprolide acetate in the oleic acid layer and the initial quantity in the pH 5.0 acetate buffer. This Example further demonstrates the evidence of the extraction of leuprolide acetate into oleic acid by partitioning methods.

Example 6

Efficacy of the Formulation by measuring plasma testosterone levels in rats

A formulation concentrate was prepared by the process described above.

Table 3 lists the ingredients and respective amounts of the ingredients used in the concentrate.

Table 3

Leuprolide Acetate	5 mg/mL (or 10 mg/mL)
Water	2% (v/v)
Ethanol	10% (v/v)
Oleic Acid	40% (v/v)
Polysorbate	40% (v/v)
Menthol	0.5% (w/v)
Prosweet	1.5% (v/v)
Methylparaben	0.1% (w/v)
BHT	0.1% (v/v)
q.s.	Tween 80

Study

A 14-day study was carried out on 25 conscious, matured Sprague-Dawley (SD) male rats, each approximately 400 grams in weight. The rats were divided into five groups of five rats each for receiving various doses. All rats were non-fasted throughout the study. The oral dosages were administered into the stomach by gavage every morning for 14 days.

The oral formulations were prepared by dispersing the formulation concentrate (5mg/mL) in adequate amount of water as set forth in Table 4 below.

Table 4

Dosage Form	Dilution	Preparation
1mg/mL	1/5	Mix 2 mL formulation with 8 mL water and vortex for 1 minute
0.5 mg/mL	1/10	Mix 1 mL formulation with 9 mL water and vortex for 1 minute
0.25 mg/mL	1/20	Mix 1 mL formulation with 19 mL water and vortex for 1 minute
0.1 mg/mL	1/50	Mix 1 mL formulation with 49 mL water and vortex for 1 minute
0.05 mg/mL	1/100	Mix 1 mL formulation with 99 mL water and vortex for 1 minute

The five groups of rats received the above dispersed oral formulations each morning for 14 days according to the schedule listed below in Table 5.

Table 5

Group #	Dose (mg/kg/day)	Number of Rats/Group
1	2.5	5
2	1.25	5
3	0.625	5
4	0.25	5
5	0.125	5

Bleeding Schedule

To assay testosterone and leuprolide acetate levels in plasma, blood was collected periodically from the tail veins of the rats. The times for bleeding, at which 0.5 mL of tail-vein blood was collected in Winetrob tubes, were scheduled so that, initially, the rats were bled before the first dosing and then 15 minutes, one hour, two hours, four hours, and eight hours after the dose was administered. On subsequent Days 1, 2, 3, 4, 5, 6, 7, 9, 11, and 14, bleeding was carried out one-half hour before dosing.

The plasma was isolated from the blood by centrifugation and analyzed for testosterone and leuprolide acetate by radioimmunoassay analysis.

Table 6 sets forth the results of the plasma testosterone levels in rats during 14 days of oral administration of the above oral formulation.

Table 6

Dose	Plasma Testosterone Levels (ng/mL)									
	2.5 mg/kg		1.25 mg/kg		0.625 mg/kg		0.25 mg/kg		0.125 mg/kg	
Time (Day)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	2.60	0.44	2.62	0.39	2.32	0.55	1.47	0.47	1.60	0.45
0.01	2.62	0.38	2.86	0.34	2.45	0.61	1.89	0.53	1.75	0.56
0.04	4.93	0.91	4.98	0.31	3.56	0.23	3.54	0.66	2.99	0.39
0.08	7.69	0.88	7.04	0.21	8.51	0.28	6.92	0.48	6.32	1.18
0.16	7.05	0.36	6.61	0.17	7.82	0.45	5.75	0.29	6.73	0.96
0.33	6.00	0.56	4.72	1.30	7.05	0.99	4.36	0.40	3.90	1.52
1.0	0.77	0.13	0.99	0.17	.091	0.09	0.71	0.15	0.41	.024
2.0	0.45	0.10	0.52	0.11	.063	0.16	0.36	0.08	0.35	0.12
3.0	0.31	0.06	0.39	0.05	0.42	0.07	0.36	0.04	0.33	0.08
4.0	0.31	0.07	0.34	0.07	0.35	0.08	0.29	0.10	0.35	0.10
5.0	0.30	0.05	0.39	0.14	0.42	0.14	0.26	0.11	0.64	0.40
6.0	0.28	0.08	0.19	0.02	0.24	0.05	0.25	0.06	0.34	0.13
7.0	0.27	0.09	0.25	0.03	0.41	0.08	0.21	0.06	0.33	0.07
9.0	0.30	0.05	0.34	0.04	0.36	0.04	0.27	0.10	0.59	0.40
11.0	0.18	0.02	0.34	0.06	0.39	0.03	0.45	0.15	0.83	0.29
14.0	0.27	0.06	0.03	0.03	0.53	0.04	0.30	0.07	0.70	0.33

The results in Table 6 demonstrate that the oral formulations of the invention are efficaceous in reducing the plasma testosterone levels in rats.

WE CLAIM:

1. A pharmaceutical composition, suitable for oral administration, comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

2. A pharmaceutical concentrate comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

3. The concentrate of Claim 2, wherein the concentrate further comprises a C_1-C_5 alcohol.

4. The concentrate of Claim 3, volume of the alcohol varies from about 0% to about 60% by volume of the concentrate.

5. The concentrate of Claim 4, wherein the volume of the alcohol varies from about 2% to about 10% by the volume of the concentrate.

6. The concentrate of Claim 2 further comprising a pH buffer.

7. The concentrate of Claim 6, wherein the pH varies from about 2 to about 8.

8. The concentrate of Claim 3, further comprising a self-emulsifying material.

9. The concentrate of Claim 2, wherein the amount of the hydrophilic drug ranges from about 1 mg to about 20 mg/mL of the volume of the concentrate.

10. The concentrate of Claim 2, wherein the hydrophilic drug is a peptide.

11. The concentrate of Claim 10, wherein the peptide is an agonist or antagonist of LHRH or a pharmaceutically acceptable salt thereof.

12. The concentrate of Claim 11, wherein the agonist or antagonist of LHRH is selected from the group consisting of

N-acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyltyrosyl-D-N^e-nicotinoyllysyl-L-leucyl-L-N^e-isopropyllysyl-L-prolyl-D-alanylamide acetate,

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate; or a pharmaceutically acceptable salt thereof.

13. The concentrate of Claim 2, wherein the fatty acid has a carbon chain ranging from 5 to 25 carbon atoms.

14. The concentrate of Claim 13, wherein the amount of the fatty acid varies from about 10% to about 99.8% of the volume of the concentrate.

15. The concentrate of Claim 14, wherein the amount of the fatty acid is about 40% of the volume of the concentrate.

16. The concentrate of Claim 2, wherein the amount of water is from 0.2% to about 20% of the volume of the concentrate.

17. A pharmaceutically acceptable soft-elastic capsule comprising a pharmaceutical concentrate, suitable for oral administration, comprising a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid and water.

18. A pharmaceutical composition concentrate, suitable for oral administration, comprising 50 mg of a hydrophilic drug, 0.2 mL of water, 1.0 mL ethanol, 4.0 mL oleic acid and 4 mL Tween-80.

19. An oral pharmaceutical composition comprising:

a pharmaceutical concentrate dispersed in an aqueous phase optionally comprising a self-emulsifying material, wherein the concentrate comprises a hydrophilic drug solubilized in a lipophilic phase comprising a fatty acid, and water.

20. The oral composition of Claim 19, wherein the aqueous phase is selected from the group consisting of milk; fruit juice; water, and a solution comprising an excipient selected from the group consisting of aspartame, glucose, mannitol, sorbitol, sugar, sucrose and lactose.

21. The oral pharmaceutical composition of Claim 19, wherein the oral pharmaceutical comprises a self-emulsifying material.

22. A process for preparing a pharmaceutical formulation concentrate suitable for oral administration comprising:

dissolving a hydrophilic drug in water and;

extracting the solubilized drug into a fatty acid.

23. The process of Claim 22, wherein the concentrate further comprises a C_1-C_5 alcohol varies from about 0% to about 60% by volume of the concentrate.

24. The process of Claim 23, wherein the volume of the alcohol varies from about 5% to about 30% by the volume of the concentrate.

25. The process of Claim 22 further comprising a pH buffer.

26. The process of Claim 25, wherein the pH varies from about 2 to about 8.

27. The process of Claim 22, further comprising a self-emulsifying material.

28. The process of Claim 22, wherein the amount of the hydrophilic drug ranges from about 1 mg to about 20 mg/mL of the volume of the concentrate.

29. The process of Claim 28, wherein the hydrophilic drug is a peptide

30. The process of Claim 28 wherein the peptide is an agonist or antagonist of LHRH or a pharmaceutically acceptable salt thereof.

31. The process of Claim 30, wherein the agonist or antagonist of LHRH is selected from the group consisting of

N-acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyltyrosyl-D-N^e-nicotinoyllysyl-L-leucyl-L-N^e-isopropyllysyl-L-prolyl-D-alanylamide acetate,

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate; or a pharmaceutically acceptable salt thereof.

32. The process of Claim 23, wherein the fatty acid has a carbon chain ranging from 5 to 25 carbon atoms.

33. A pharmaceutical composition concentrate, suitable for oral administration, prepared by the process comprising:

dissolving a hydrophilic drug in water and;

extracting the solubilized drug into a fatty acid.

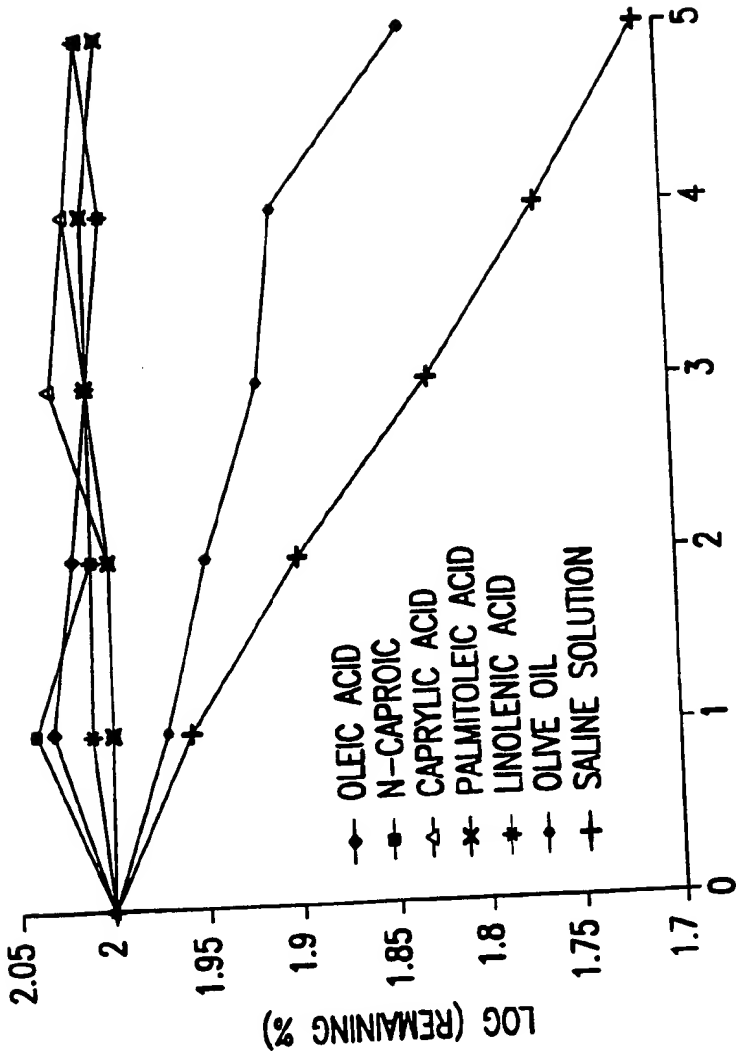

LOG (REMAINING %)
2.05
2
1.95
1.9
1.85
1.8
1.75
1.7
0
1
2
3
4
5
TIME (h)
OLEIC ACID
N-CAPROIC
CAPRYLIC ACID
PALMITOLEIC ACID
LINOLENIC ACID
OLIVE OIL
SALINE SOLUTION

FIG.1

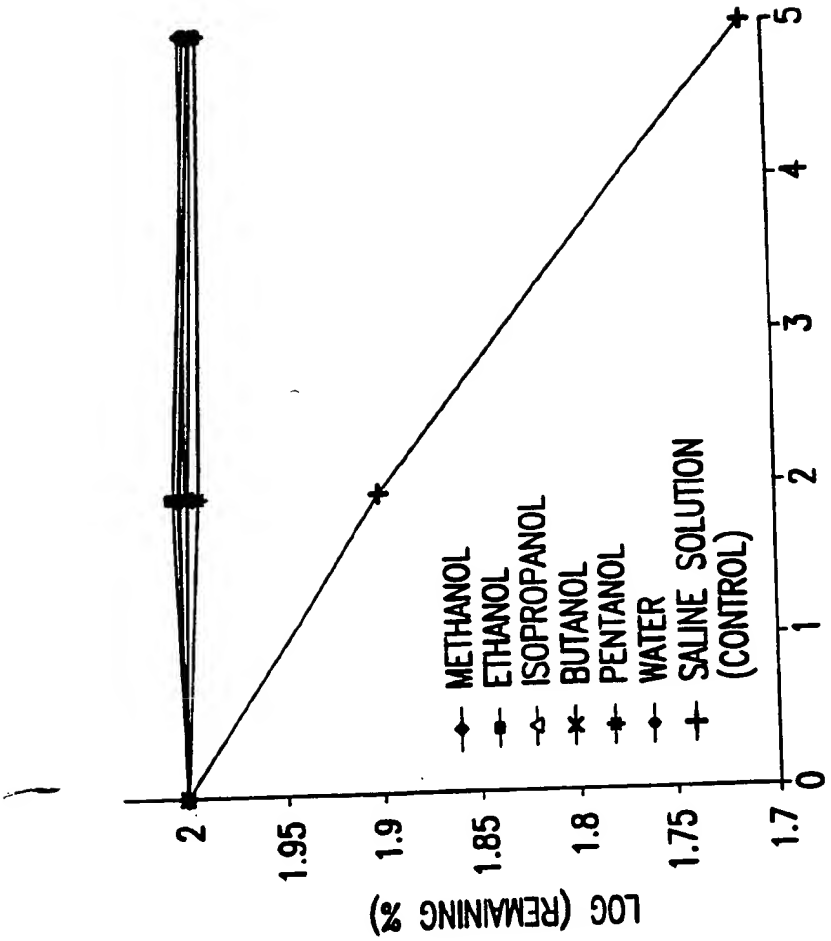

LOG (REMAINING %)
2
1.95
1.9
1.85
1.8
1.75
1.7
0
1
2
3
4
5
TIME (h)
METHANOL
ETHANOL
ISOPROPANOL
BUTANOL
PENTANOL
WATER
SALINE SOLUTION
(CONTROL)

FIG.2

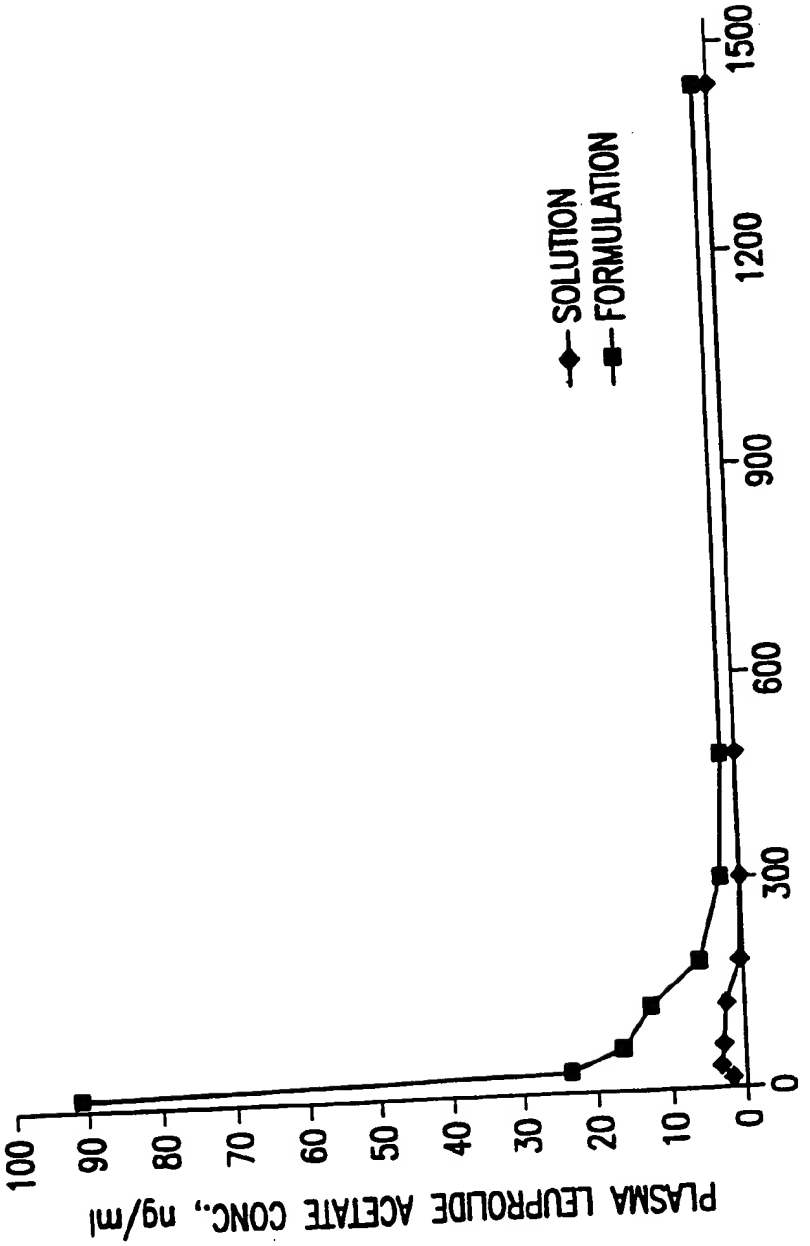

PLASMA LEUPROLIDE ACETATE CONC., ng/ml
100
90
80
70
60
50
40
30
20
10
0
0
300
600
900
1200
1500
TIME (min)
SOLUTION
FORMULATION

FIG.3

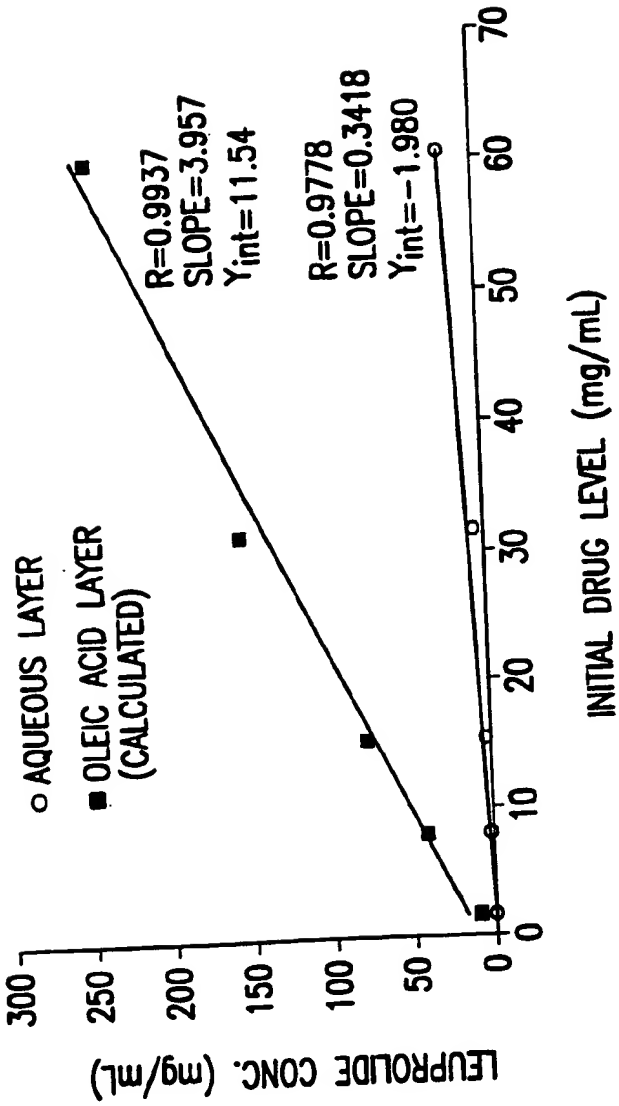
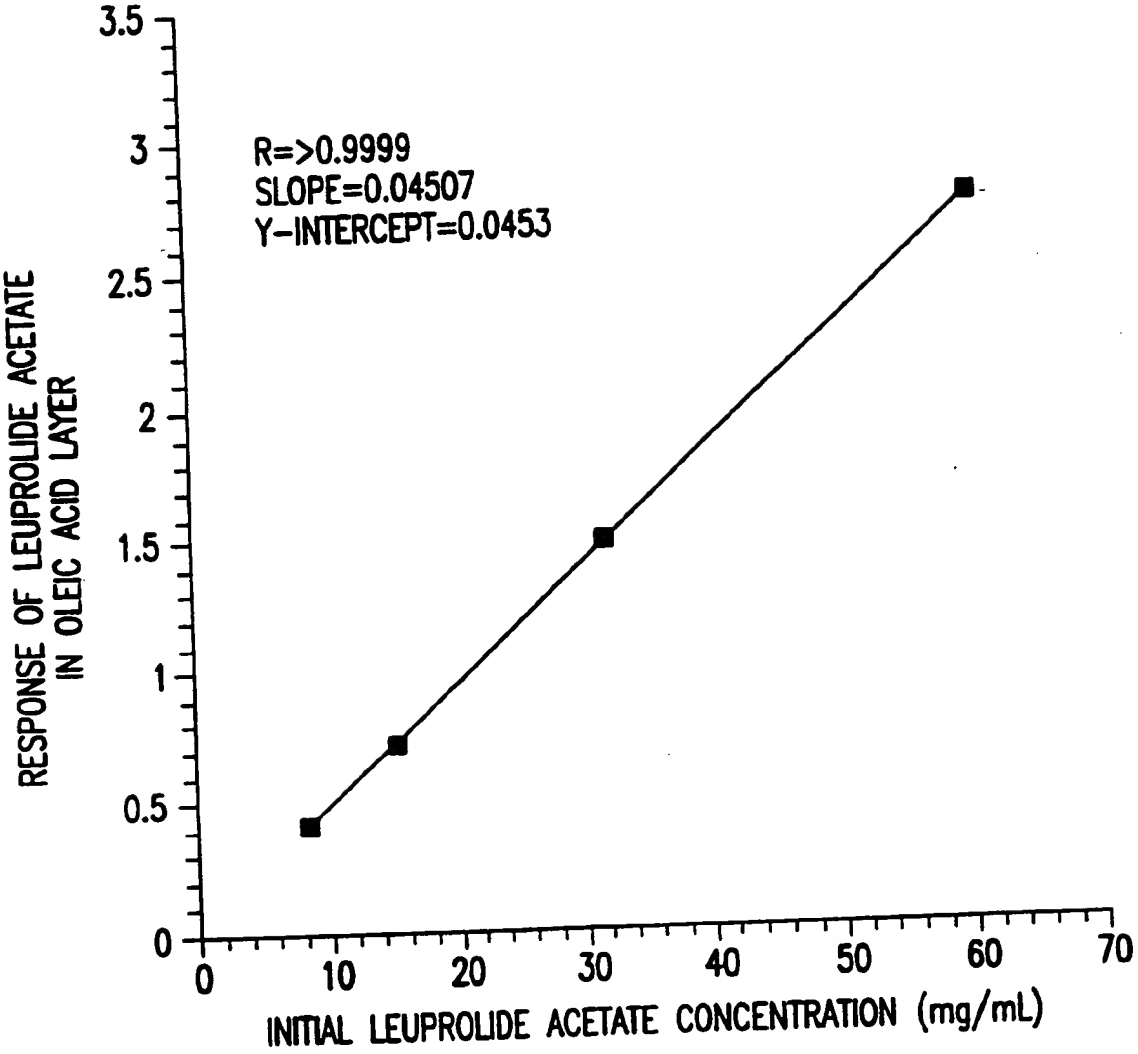

LEUPROLIDE CONC. (mg/mL)
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
INITIAL DRUG LEVEL (mg/mL)
○ AQUEOUS LAYER
■ OLEIC ACID LAYER (CALCULATED)
R=0.9937
SLOPE=3.957
Yint=11.54
R=0.9778
SLOPE=0.3418
Yint=-1.980

FIG.4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SLOPE=0.04507
Y-INTERCEPT=0.0453
RESPONSE OF LEUPROLIDE ACETATE IN OLEIC ACID LAYER
INITIAL LEUPROLIDE ACETATE CONCENTRATION (mg/mL)
0
0.5
1
1.5
2
2.5
3
3.5
0
10
20
30
40
50
60
70

FIG.5